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# Predictors of re-hospitalisation in a naturalistic cohort of patients with bipolar affective disorder

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**Running title:** Antidepressants are not associated with **re-admission**

## **Abstract**

There has been only limited research into predictors of readmission in bipolar disorder. We undertook a one year follow-up of patients discharged from a single mental health unit following admission for treatment of an acute bipolar episode. Of 519 patients followed-up for one year, 167 (32.2%) were re-admitted. There was no association between readmission and any drug regimen. Prescription of antidepressants at discharge was not associated with increased risk of re-admission (OR 0.99, 95% CI 0.98, 1.01). Amongst demographic factors, only smoking (OR 1.75; 95% CI 1.14, 2.75) and being aged 42-53 years (OR 1.99, 95% CI 1.15, 3.43) conferred an increased risk of re-admission. Individually optimised drug treatment regimens are equally effective in practice. It is not clear why smoking is associated with re-admission.

**Keywords:** Antidepressants, antipsychotics, mood stabilisers, bipolar disorder, smoking

## Introduction

Bipolar Disorder (BD) is a complex and life-long condition that requires wide-ranging clinical interventions, the mainstay of which are prescribed medications. In determining which drugs to prescribe, clinicians often look to guidelines based on comprehensive meta-analyses of controlled trials. These studies indicate the most effective single treatments in mania (Cipriani *et al.*, 2011), bipolar depression (Taylor *et al.*, 2014) and in the prophylaxis of relapse in BD (Ghaemi *et al.*, 2008; Vieta *et al.*, 2011). There is rather less known about outcomes from the use of combinations (Smith *et al.*, 2007) and older drugs, whether alone or in combination (Tohen *et al.*, 2001).

Formal clinical trials tell us about efficacy (what can work in trials) rather than effectiveness (what does work in practice). The latter is evaluated in naturalistic, non-interventional studies of normal clinical practice. In BD, as in other conditions, these studies take two forms: database studies which include large number of patients but have limited information on clinical or demographic detail and observational studies which more closely follow a smaller number of patients, often from a single healthcare unit.

There are numerous studies of both kinds in BD (Fekadu *et al.*, 2006; Hayes *et al.*, 2016; Kim E. *et al.*, 2009; Peselow *et al.*, 2016) but few of these address the real-life complexity of BD treatment (patients on multiple drug regimens are often excluded) or outcomes in people discharged from hospital following an acute episode (most are studies of out-patients).

Here we report on our non-exclusive study of patients discharged from our hospital on a wide range of drug regimens in which we aimed to uncover moderators of outcome following discharge. The aim of the study was to determine factors associated with an increased risk of readmission following discharge from hospital after treatment for an acute bipolar episode.

## Materials and Methods

All in-patient admissions which occurred between January 1<sup>st</sup> 2010 and 31<sup>st</sup> December 2011 and were formally allocated an F30 (manic episode) or F31 (Bipolar Affective Disorder) ICD-10 diagnosis (at admission or discharge) were identified from our NHS Trust's anonymised Clinical Record Interactive Search (CRIS) system. Detailed patient information was extracted from the Trust's electronic Patient Journey System (ePJS).

We tracked outcomes in all patients identified from discharge until re-admission or, if not re-admitted, for up to one year. Our primary outcome was re-admission to hospital.

### Drug regimens

We recorded all drugs prescribed at discharge without an *a priori* view on how these regimens would be later classified. We were particularly interested in the effects of antidepressant prescription on re-admission and determined to analyse outcome with those prescribed any antidepressant versus no antidepressant should there be sufficient subjects prescribed antidepressants. Other regimens were also classified *post hoc* having viewed the range of regimens recorded.

### Demographic details

We recorded all patient-level data reliably available to use from the ePJS system (gender, age, ethnicity, diagnosis) and other data deemed *a priori* as factors of interest (smoking, BMI, illicit drug or alcohol use)

### Statistical analysis

Descriptive statistics were calculated for all subjects. Readmission was defined as being readmitted within one year of discharge. Unadjusted differences in characteristics between readmission status were compared using independent t-test for continuous data and chi-squared test for categorical data. The time to readmission curve was plotted using the method of Kaplan-Meier. Associations between subject characteristics and readmission

status were then explored using logistic regression. The number of readmissions to variable ratio was lower than the recognised minimum of 10.(Harrell, 2001) In order to avoid over-fitting and increasing the standard errors of coefficients the LASSO (Least Absolute Shrinkage and Selection Operator) method to shrink regression coefficients towards the null value was used.(Tibshirani, 2011) The approach is recommended over using stepwise approached to variable selection or univariate screening techniques.(Pavlou *et al.*, 2015) Dummy variables were constructed for nominal variables. The association of 'medication on discharge' with 'readmission within one year' was examined using two approaches. The first model included medication categorised by drug class and use of depot, the second model included individual drugs of interest and the generation (first or second) of antipsychotic. The assumption of linearity on the logit scale was examined by plotting the logit of the proportion on readmission across categorised groups for age. As the linearity assumption was not deemed reasonable the variable was categorised based on quartiles and treated as a dummy variable with the lowest category as reference. Model specification was examined using the link-test and the observed versus predicted values (calibration) was examined using the Hosmer and Lemeshow's goodness-of-fit test. All analysis were performed in Stata version 13.

## Results

A total of 716 patients were identified via CRIS, 519 patients met the inclusion criteria of F30 or F31 diagnosis. Patients were excluded if a F30 or F31 diagnosis was not met (n=98); as were patients who died before discharge (n=6); patients without complete records for data extraction (n=3); patients who were discharged from Trust services (lost to follow-up) (n=10) and those patients who were admitted in 2010 and re-admitted in 2011 (i.e. duplicates) (n=80).

Overall, 167 of 519 patients (32.2%) were readmitted during the year's follow-up (Figure 2). Smoking was statistically associated with increased likelihood of readmission – 69.5% of those readmitted were smokers but only 56.8% of those not readmitted ( $p=0.006$ ). Those re-admitted also had a higher mean BMI (29.5) than those not re-admitted (26.0) ( $p<0.001$ ) but these data were available only for 206 subjects. Table 1 describes the cohort's individual patient characteristics.

No individual medication or multiple medication regimen was statistically associated with re-hospitalisation (Table 2) and numerically outcomes were very similar. Overall, 69 patients (13.8%) were discharged on an antidepressant but this did not affect risk of re-admission ( $p=0.962$ ). Amongst these patients a minority were prescribed antidepressants alone (n=4; all SSRIs) but most (n=65; 34 SSRIs, 14 SNRIs, 10 mirtazapine, 5 amitriptyline and 2 reboxetine) an antidepressant alongside a mood stabiliser or antipsychotic.

In the logistic regression model (Table 3) the odds ratio for readmission was statistically increased for those aged 42-53 years (OR 1.99 CI 1.15-3.43,  $p=0.014$ ), and for smokers (OR 1.75, CI 1.14-2.69,  $p=0.010$ ). No individual drug or drug combination was associated with increased or decreased odds of re-admission and none approached statistical significance. Antidepressant prescription was not associated with any change in risk of readmission and any clinical significant change was excluded - OR for readmission for those prescribed no antidepressant vs those prescribed any antidepressant was 0.99 (CI 0.98-1.01  $p=0.99$ ).

## Discussion

In our cohort of consecutive patients discharged from hospital with a diagnosis of mania or bipolar disorder, smoking status, higher body mass index and being aged 42-53 years were associated with an increased risk of re-admission. No individual drug or drug regimen, including the prescription of antidepressants, was associated with altered risk of re-admission. Overall, just less than a third of patients were re-hospitalised in the year-long follow-up.

The re-hospitalisation rate in this study is (32.2%) is somewhat higher than that observed in other studies. In an analysis of the US-based naturalistic STEP-BD study, 28.8% of 858 participants relapsed within one year of recovery.(Perlis *et al.*, 2006) In an analysis of naturalistic and controlled studies (Vazquez *et al.*, 2015) the yearly recurrence rates were 26.3% and 21.9% respectively. However, bipolar relapse or recurrence does not always result in rehospitalisation: in one analysis (Hong *et al.*, 2010) only 60% of relapsers were admitted (although not all had been admitted for the index episode). Comparative data for re-hospitalisation suggest, for example, that around 10% of treated patients are re-admitted within 90 days (Kim E., *et al.*, 2009) and 17% to 25% over one year (Patel *et al.*, 2005; Woo *et al.*, 2014). The last two figures are most relevant to our findings as both measured time from hospital discharge to re-admission (although the first included only first episode patients). The reasons for our relatively high readmission rate are difficult to determine **precisely** although our particular environment – patients treated in a publicly funded health system in a socially deprived urban context – is certainly relevant **as is the high prevalence of substance misuse, especially skunk-like cannabis (Di Forti *et al.*, 2015)**. Treatment in a specialised mood disorder clinic early in the course of bipolar disorder has been shown to substantially reduce readmission to psychiatric hospital and increase satisfaction with care (Kessing *et al.*, 2013) although, somewhat surprisingly, this approach has not yet been widely adopted.

Smoking in bipolar disorder has previously been linked to a greater severity of symptoms, poorer functioning and a history of suicide attempts (Ostacher *et al.*, 2009; Ostacher *et al.*, 2006; Waxmonsky *et al.*, 2005). The reasons for this association are not clear but smoking



status may be linked to impulsivity (Ostacher, *et al.*, 2009; Ostacher, *et al.*, 2006), a higher prevalence of ADHD symptoms (Waxmonsky, *et al.*, 2005) and induction of drug metabolising enzymes (Kroon, 2007). In fact, smoking status may simply be a marker for poor prognostic indicators in BAD: rapid-cycling, substance misuse and co-morbid psychiatric conditions are each associated with smoking (Waxmonsky, *et al.*, 2005).

Higher body weight has also previously been linked to worsened outcomes in bipolar disorder (Calkin *et al.*, 2009; Kim B. *et al.*, 2008; Maina *et al.*, 2008). Again, the reasons for this remain uncertain but certainly higher body weight would mean higher doses of drugs would be needed. Also, increased BMI may reflect relatively greater disturbance in the HPA axis which in turn may be associated with a greater disease severity (Maina, *et al.*, 2008). The age range found in our study (being aged 42-53 years) to be most associated likely reflects a peak age of risk for readmission due to the progressive nature of bipolar disorder for many patients (Angst & Sellaro, 2000) coupled with increased death rate causing attrition from this age (Grande *et al.*, 2016).

We did not find any associations between drug therapy and re-hospitalisation, although we had hypothesised that those discharged on antidepressants would be seen to have a worse outcome (particularly relapse into mania leading to readmission), as suggested by randomised controlled trials (Ghaemi, *et al.*, 2008). The absence of any associations with re-admission for any drug or drug regimen was also surprising given the results of previous studies (Hayes, *et al.*, 2016; Kim E. *et al.*, 2011; Peselow, *et al.*, 2016). There are at least **three** possible explanations for our findings. First, it may have been that we had insufficient subjects (and therefore statistical power) to demonstrate differences in a (low power) binary outcome such as readmission. Against this is the observation that none of our findings approached significance and all were remarkably numerically similar: there were no particular trends observed, **(with two exceptions of poor outcome with aripiprazole and depot antipsychotics)**. Second, it is possible that by including those subjects on complex medication regimens we 'evened-out' differences between individual drugs' therapeutic effects. Third (and perhaps most likely), it may be that clinically optimised complex regimens **(which can be fine-tuned following discharge)** give broadly similar outcomes in practice, as

opposed to the un-optimised, randomly assigned, rigid treatments of controlled trials. For example, the co-prescription of a mood-stabilising drug might mitigate the manic switching propensity of antidepressants – 65 of 69 subjects in our study prescribed antidepressants also received a classical mood-stabiliser or mood-stabilising antipsychotic. However, this cannot be said with any certainty as we did not record reason for admission following discharge (although nearly all of our admissions are for mania or hypomania). Uncertainties remain about the benefits and harms of antidepressant use in bipolar disorder (Pacchiarotti *et al.*, 2013) but our data suggest that these should be further investigated in naturalistic studies. Our data also weakly suggest a negative effect for depot antipsychotics (39.4% of those on depot were re-admitted). However, this was not a statistically significant association and may reflect selection bias: the naturalistic use of depots in patients known to be poor compliers. Likewise the relatively poor outcome with aripiprazole (42.1% readmitted) did not approach statistical significance in any analyses.

Drug regimens prescribed to patients discharged from hospital after admission for acute mania does not appear to affect the risk of rehospitalisation. The adverse effect of smoking on rehospitalisation is striking and requires further investigation to determine to what extent smoking directly influences readmission.

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**Declaration of Interest**

DT has received speaker honoraria from Janssen, Servier, Otsuka and Lundbeck and is on the following advisory boards: Servier, Lundbeck and Sunovion. Research funding has been received from Janssen, Lundbeck and BMS. AY has received speaker honoraria and is on the advisory boards for the following companies with drugs used in affective and related disorders: Astrazenaca, Eli Lilly, Janssen, Lundbeck, Sunovion, and Servier. No share holdings in pharmaceutical companies. Lead Investigator for Embolden Study (AZ), BCI Neuroplasticity study and Aripiprazole Mania Study. Investigator initiated studies from AZ, Eli Lilly, Lundbeck, Wyeth. Grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK). MOH and VC declare no competing interests.

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